HPV Immunization: Separating the Myths from Reality

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Objective

- To discuss the development of the HPV vaccine and the effects on HPV related malignancies

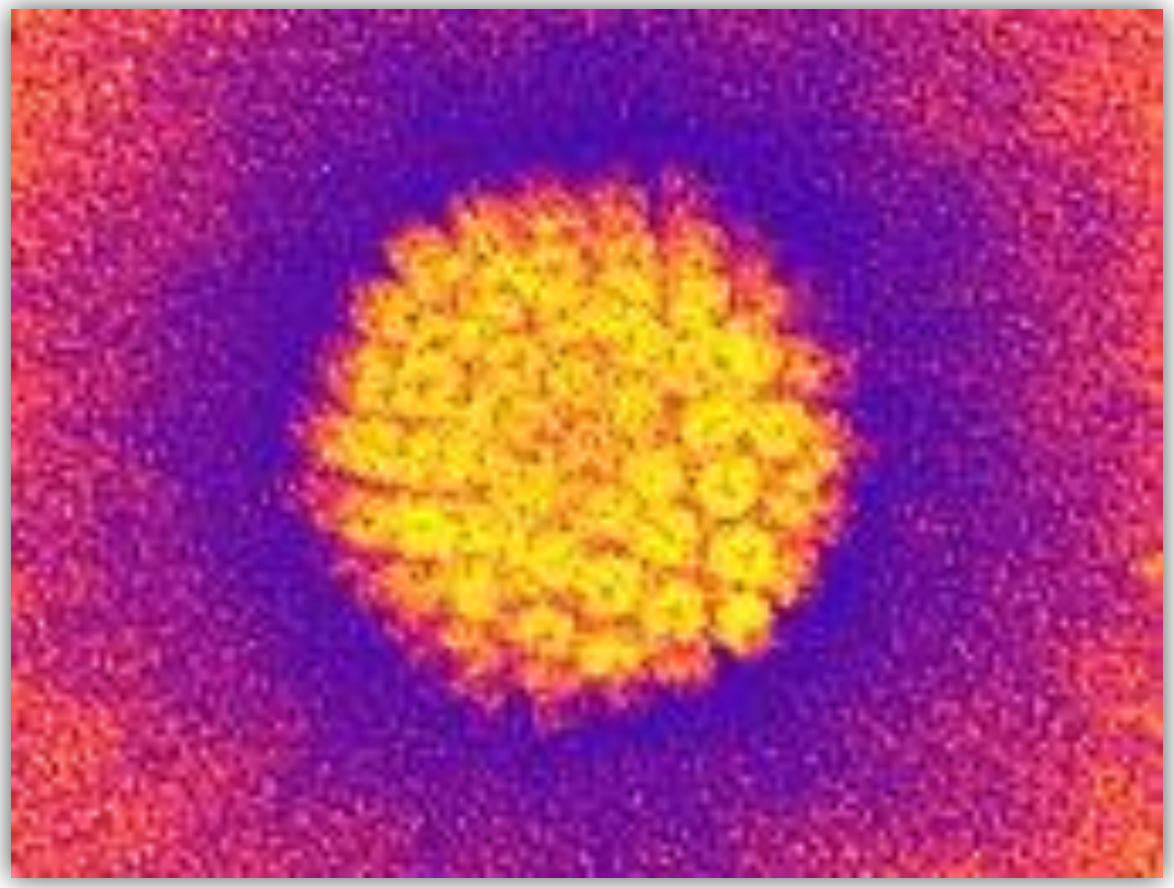
Outline

- Human Papilloma Virus (HPV)
  - Background, Natural History of Infection
- HPV Vaccine
  - Initial Developments and Clinical Trials
  - Dispelling the Myths
  - International Success Stories
  - What We Can Do

Human Papilloma Virus (HPV)

Background and Natural History of Infection

What is HPV?



Human Papilloma Virus

- Double stranded circular DNA virus
- Over 100 strains identified to date

TABLE 1
HPV classification

High-risk	HPV types
Carcinogenic[a]	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Probably carcinogenic[a]	68
Possibly carcinogenic[a]	26, 53, 66, 67, 70, 73, 82
Tested for in commercially available detection systems	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68
Low-risk	6, 11, 40, 42, 43, 44, 54, 61, 72, 81, 89

HPV, human papillomavirus.

[a] Data adapted from Bouvard V, Baan R, Straif K, et al.[23]

Erickson. HPV review. Am J Obstet Gynecol 2013.

HPV Related Diseases

Non-Cancer

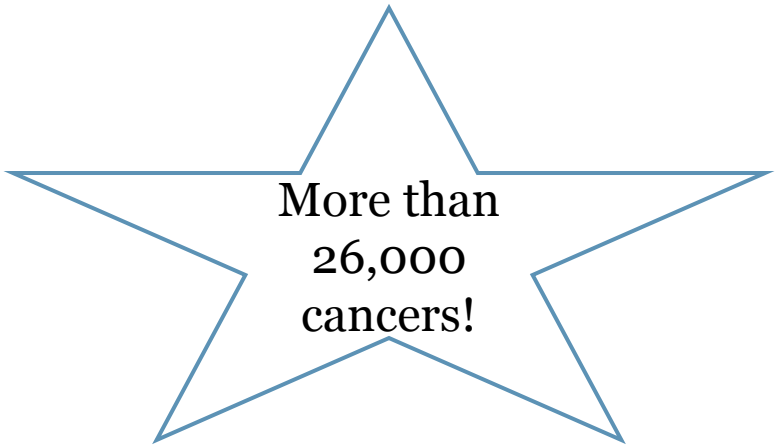
- Ano-genital Warts
- Recurrent Respiratory Papillomatosis

Cancer

- Cervical Cancer
- Vaginal Cancer
- Vulvar Cancer
- Penile Cancer
- Anal Cancer
- Oropharyengeal Cancer

Just in the U.S. ~ HPV implicated in:

- 10,300 cervical cancers
- 2,100 vulvar cancers
- 500 vaginal cancers
- 600 penile cancers
- 2,800 anal cancers in women
- 1,500 anal cancers in men
- 1,700 oropharyngeal cancers in women
- 6,700 oropharyngeal cancers in men



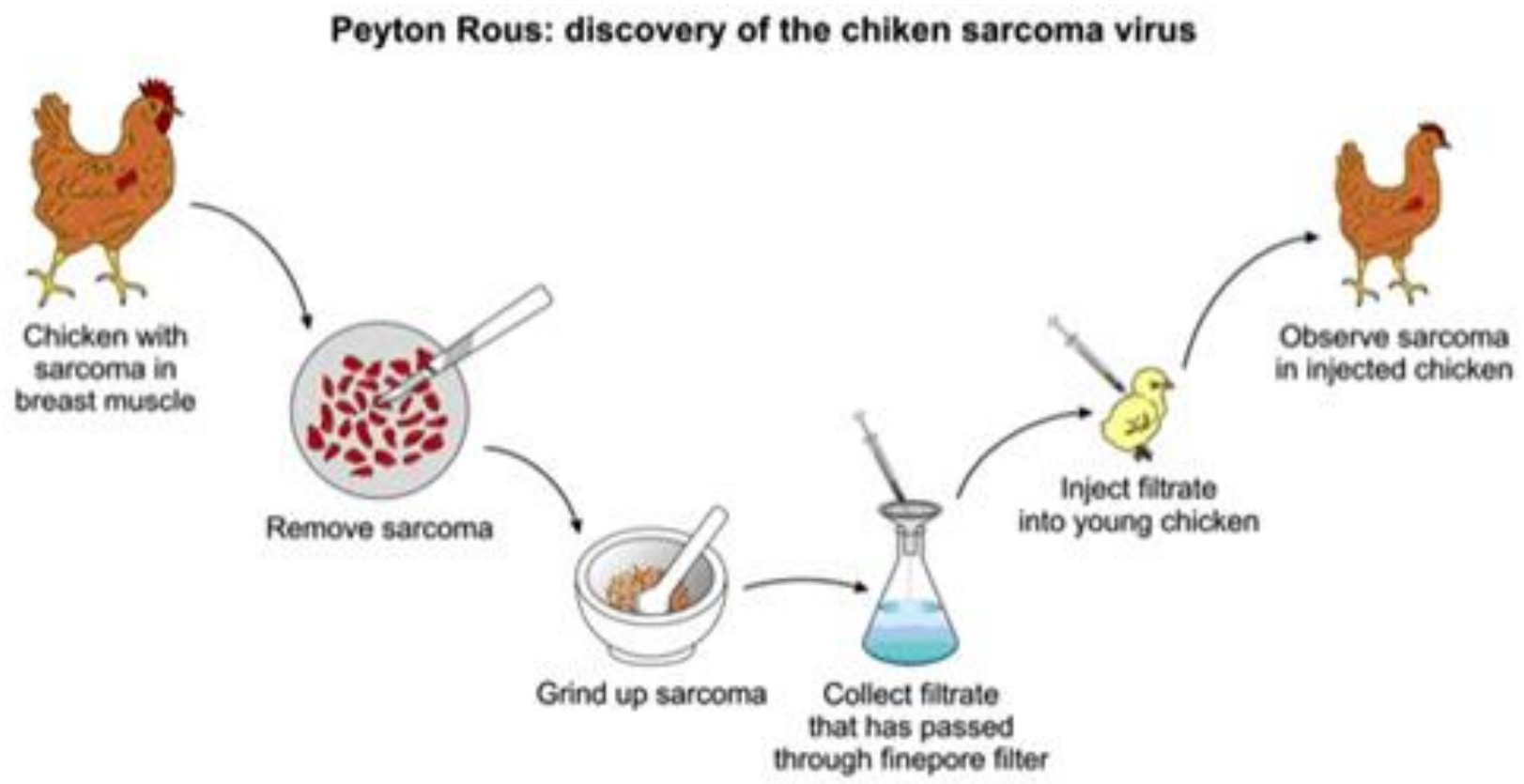
…EVERY YEAR!

http://www.cdc.gov/std/hpv/stdfact-hpv.htm

Georgios Papanicolaou (1883-1962)

- In 1923, reported the ability to see malignant cervical cells under the microscope
- “Non-invasive” method
- Screening has decreased cervical cancer incidence and mortality

Rous Sarcoma Virus (1911)

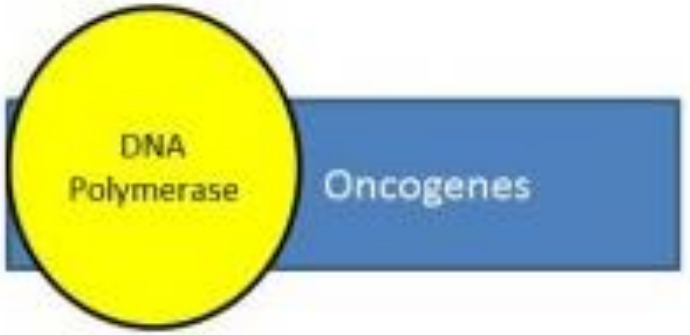


Weinberg (2013) The Biology of Cancer

For Cancer to Occur

Tumor Suppressor Genes (TSGs) are turned 'OFF'

Oncogenes are turned 'ON'



Pathway to HPV Discovery

- German Cancer Research Center (1983-84)
  - Identification of HPV in cervical tumors
- NCI researchers (1989)
  - HPV16 causes cancer-like traits *in vitro*
- NCI & Albert Einstein College of Medicine (1993)
  - Epidemiologic studies
  - HPV responsible for premalignant changes in pap smear and development of most cervical cancers

https://www.cancer.gov/research/progress/discovery/hpv-vaccines

HPV Genome

E1: DNA helicase/NTPase

E2: Transcriptional *trans*-modulator, replication control

E4: Cytokeratin disruption

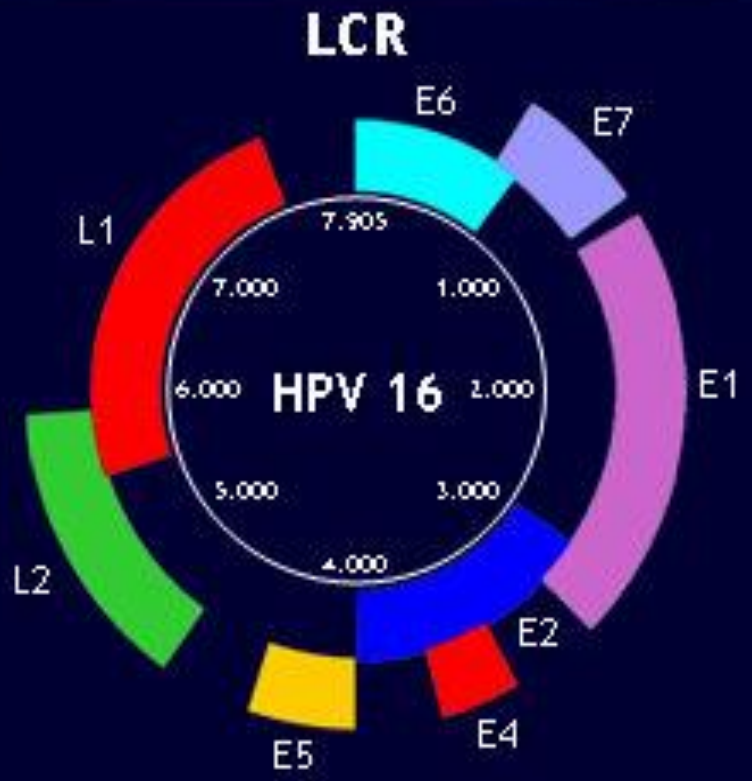
E5: Cell proliferation (binds PDGF receptor)

E6: Transforming protein (binds p53)

E7: Transforming protein (binds pRb)

L1: Major capsid protein

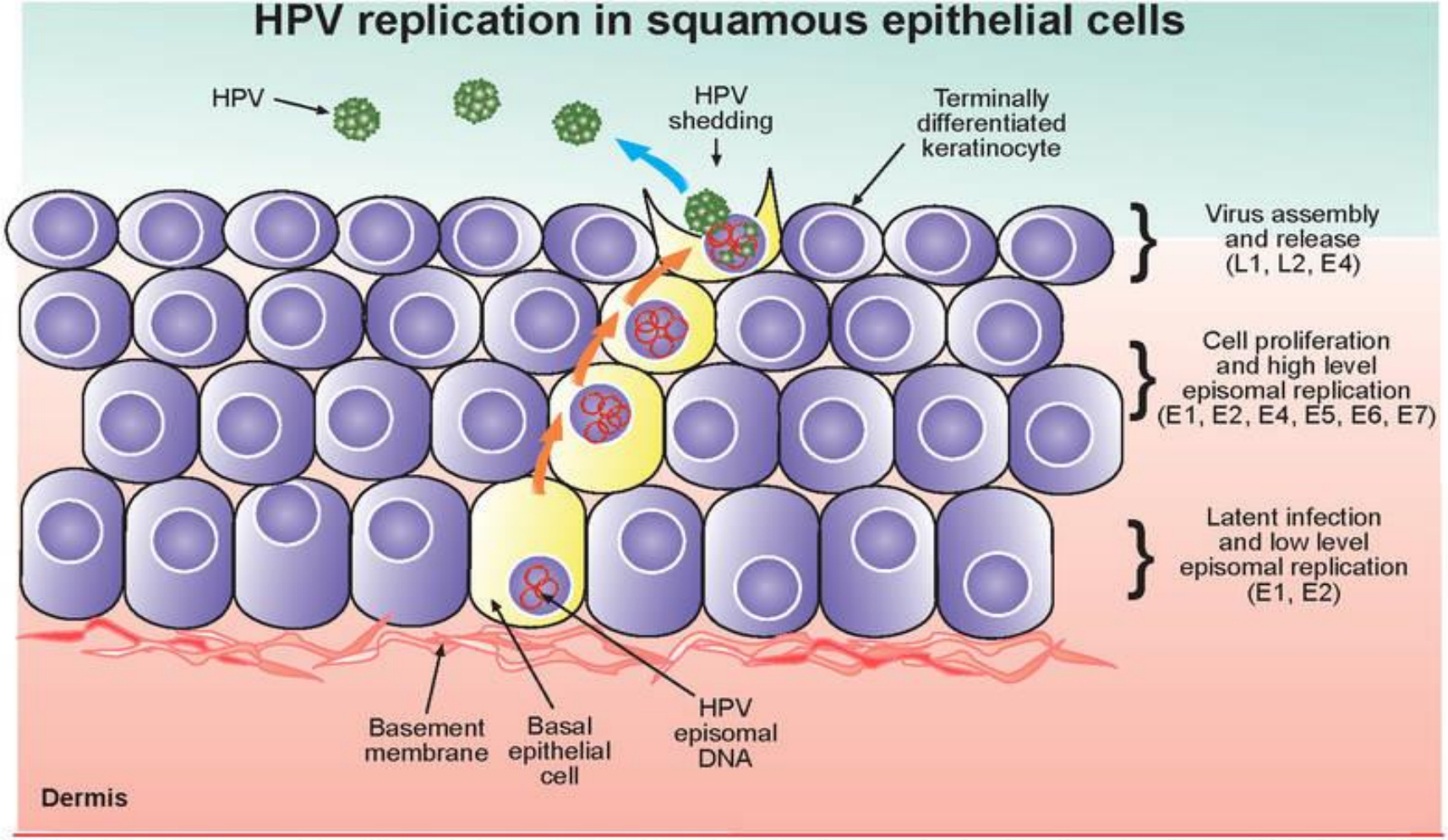
L2: Minor capsid protein



LCR=locus control region; NTPase=nucleoside 5'-triphosphatase; PDGF=platelet-derived growth factor.

Doorbar J. *Clin Sci (Lond)*. 2006;110:525-541.

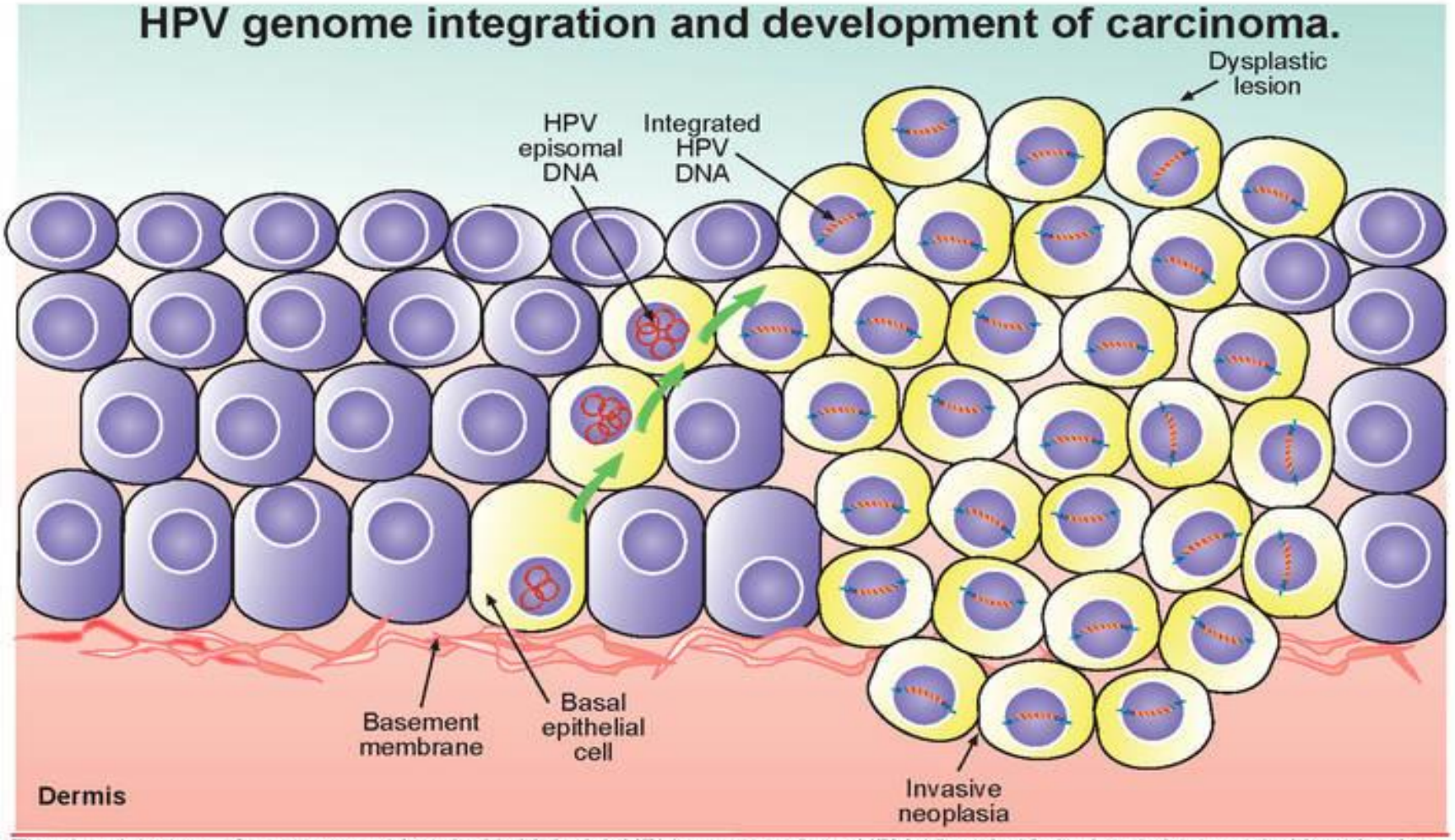
http://www.medscape.org/viewarticle/558452



HPV takes advantage of the differentiation pathway of keratinocytes that are destined to die naturally (anoikis). Since HPV is not cytolytic and does not cause viraemia, there is no inflammation and subsequent activation of the immune system. Infection of basal epithelial cells establishes a latent infection with low level replication of the viral episome and minimal viral protein expression. Following differentiation of the keratinocyte, early HPV genes are expressed and the viral episome is further amplified to higher copy numbers. Viral late protein expression and virus assembly occurs during terminal differentiation of the keratinocyte and viruses are shed from the outermost layer of epithelial cells.

immunopaedia.org

http://immunopaedia.org.za/index.php?id=799

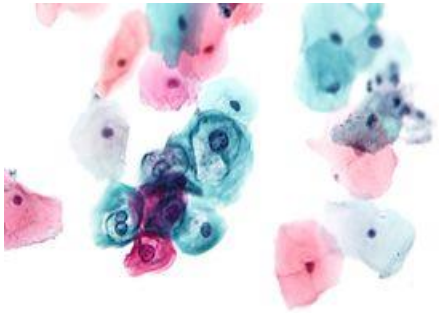


The development of cancer associated with high risk HPV types, such as HPV-16 and -18, is dependent on viral inactivation of cellular tumour suppressor proteins p53 and retinoblastoma protein (pRb) followed by the accumulation of DNA damages. Inactivation of p53 and pRb is mediated by viral oncoproteins E6 and E7. Increased synthesis of E6 and E7 occurs following chromosomal integration of HPV genomes carrying a disrupted E2 gene that is required for regulation of E6 and E7 transcription. In the absence of cellular p53, DNA damages can accumulate without repair and the removal of pRb allows cells with DNA damages to undergo cell division. Together these factors can promote the generation of a cell with a malignant phenotype although the process can take several years to develop.

immunopaedia.org

http://immunopaedia.org.za/index.php?id=800

HPV and Cervical Cancer

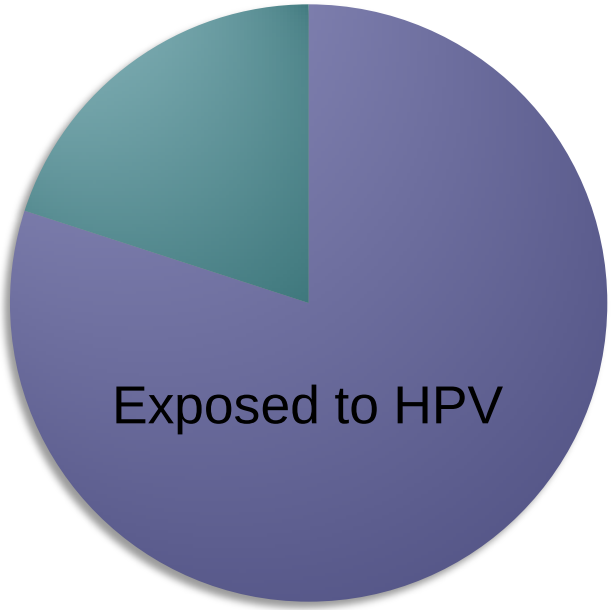


- HPV as the underlying cause of cervical cancer
  - ***Only accepted within last 20 years***
    - Journal of the National Cancer Institute (1993-1995)
    - NIH consensus Conference on Cervical Cancer (1996)
    - World Health Organization/European Research Organization on Genital Infection and Neoplasia (1996)

How Common Is HPV?

- Most men and women who have had sex have been exposed to HPV *at some point* in their lifetime.

Up to 80% of all sexually active women and men have been exposed to HPV by the age of 50.



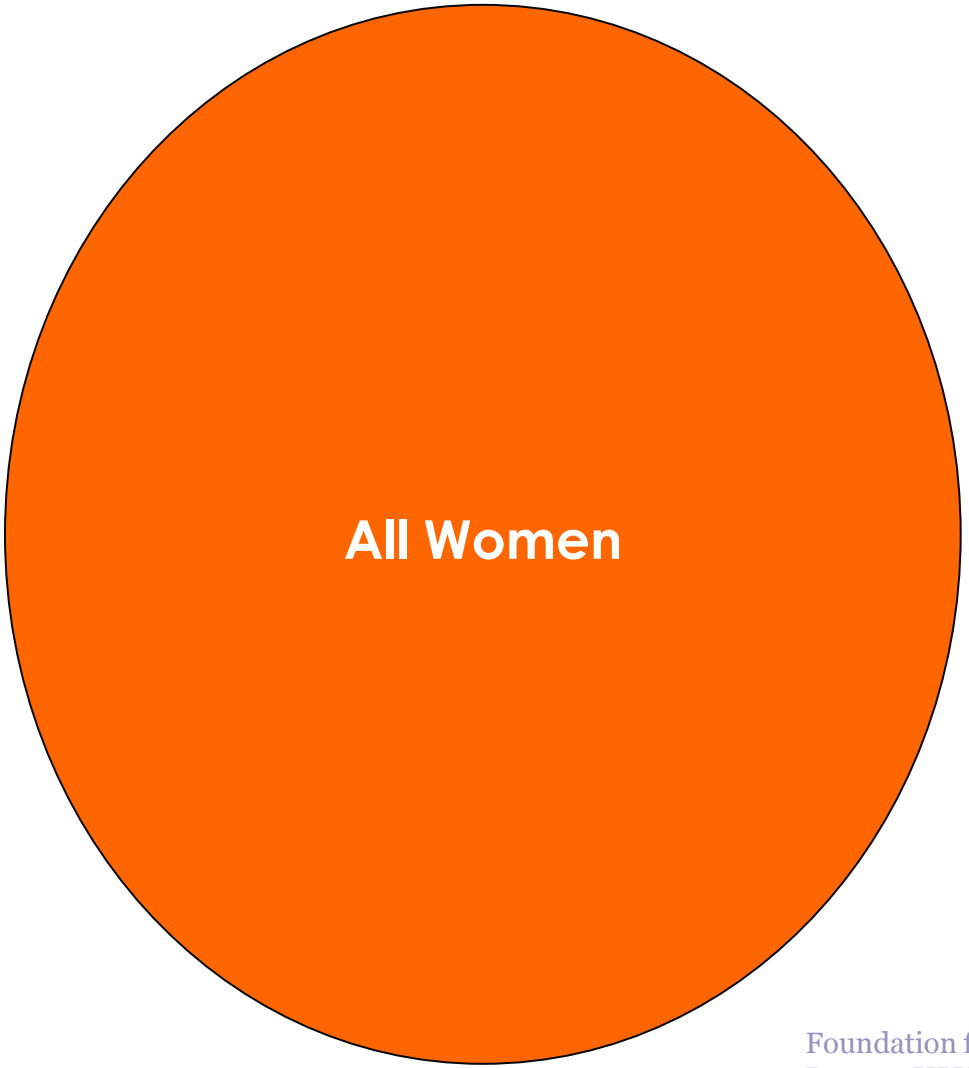
Foundation for Women's Cancer, Vaccines to Prevent HPV-Associated Diseases (2013)

How is HPV Transmitted?

- HPV is transmitted to both men and women through sexual intercourse and sexual contact.
- Abstinence *(including no touching!)* is the only way to prevent infection.
- Regular condom use can also help decrease the spread of HPV as well as other sexually transmitted infections.

Reference: Winer RL et al. Condom Use and the risk of genital human papilloma virus infection in young women. N Engl J Med. 2006 Jun 22:354(25) 2645-54.

HPV and Cervical Cancer



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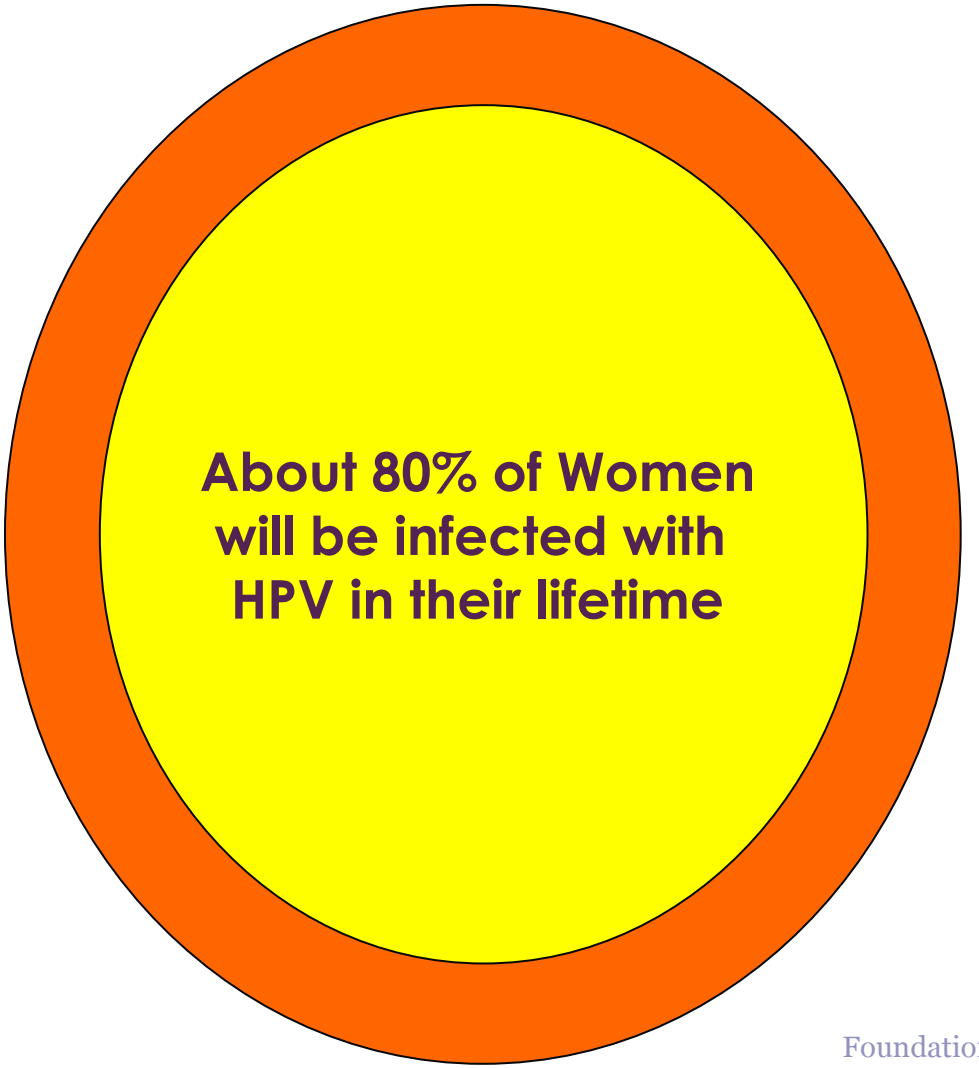
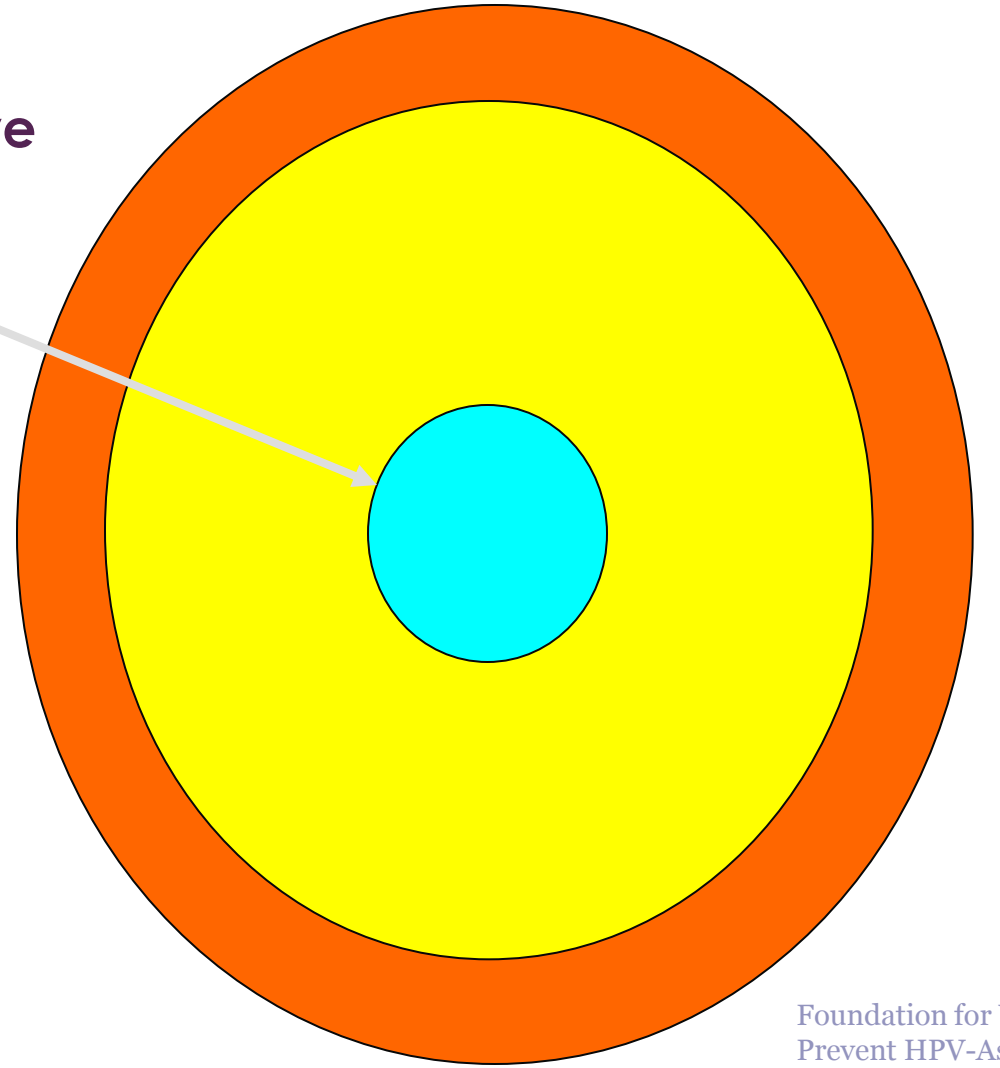
HPV and Cervical Cancer



Foundation for Women's Cancer, Vaccines to Prevent HPV-Associated Diseases (2013)

HPV and Cervical Cancer

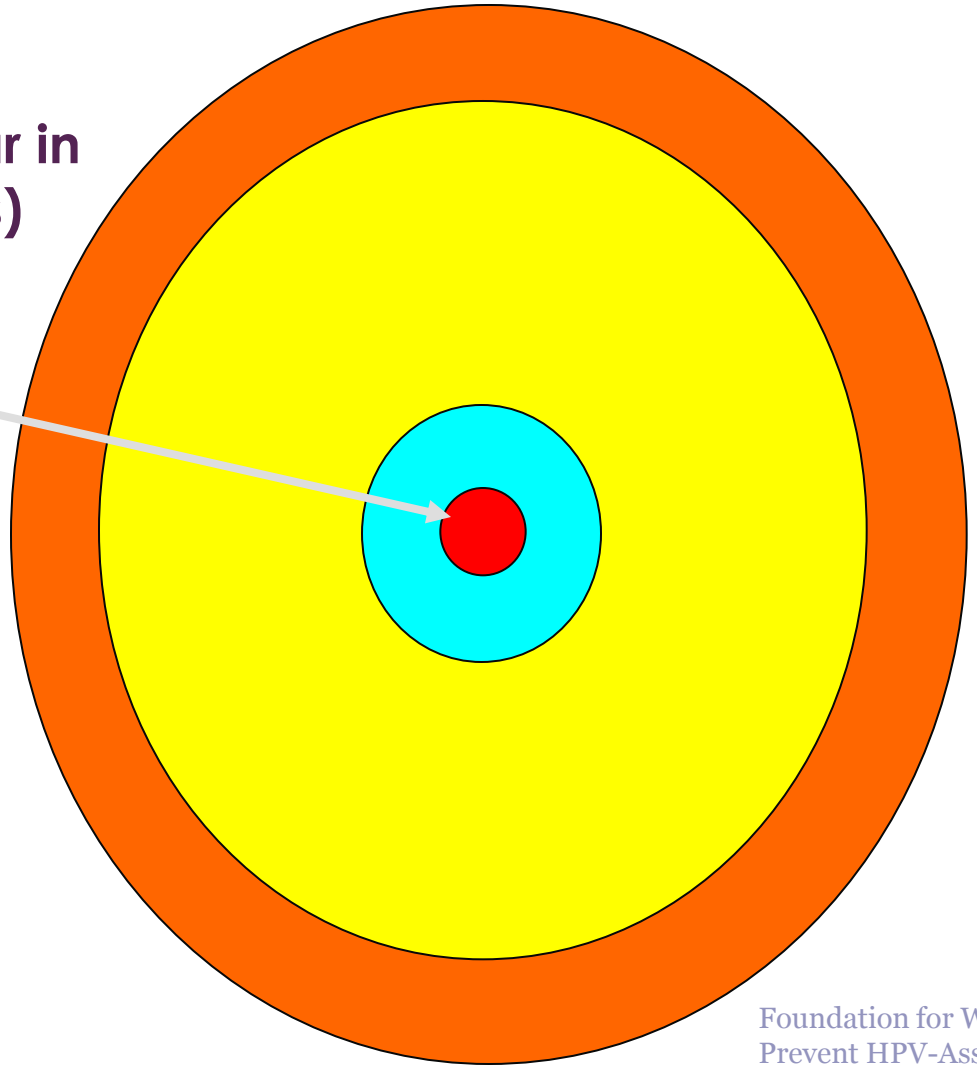
About 7% of Women will have an abnormal Pap test



Foundation for Women's Cancer, Vaccines to Prevent HPV-Associated Diseases (2013)

HPV and Cervical Cancer

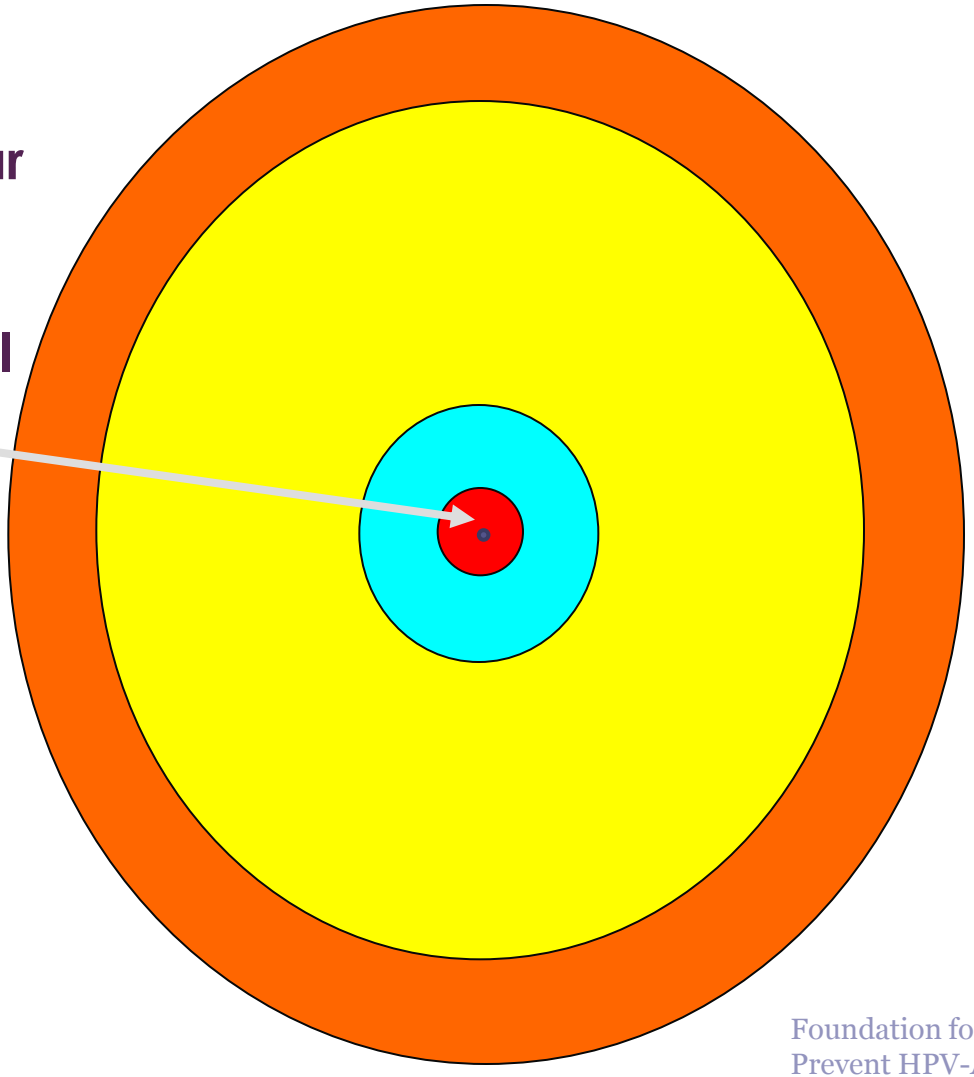
About 300,000 women (per year in the United States) will have a high grade precancerous lesion



Foundation for Women's Cancer, Vaccines to Prevent HPV-Associated Diseases (2013)

HPV and Cervical Cancer

About 11,000 Women (per year in the United States) will develop cervical cancer



Foundation for Women's Cancer, Vaccines to Prevent HPV-Associated Diseases (2013)

HPV Vaccine

Initial Development and Clinical Trials

Initial Development

- Douglas Lowy & John Schiller, PhD

"When we started this work, there was no greater optimism for an HPV vaccine than there was for an HIV vaccine. In fact, there was skepticism that it could work at all.

- John Schiller, PhD

https://www.cancer.gov/research/progress/discovery/hpv-vaccines

HPV Genome

E1: DNA helicase/NTPase

E2: Transcriptional *trans*-modulator, replication control

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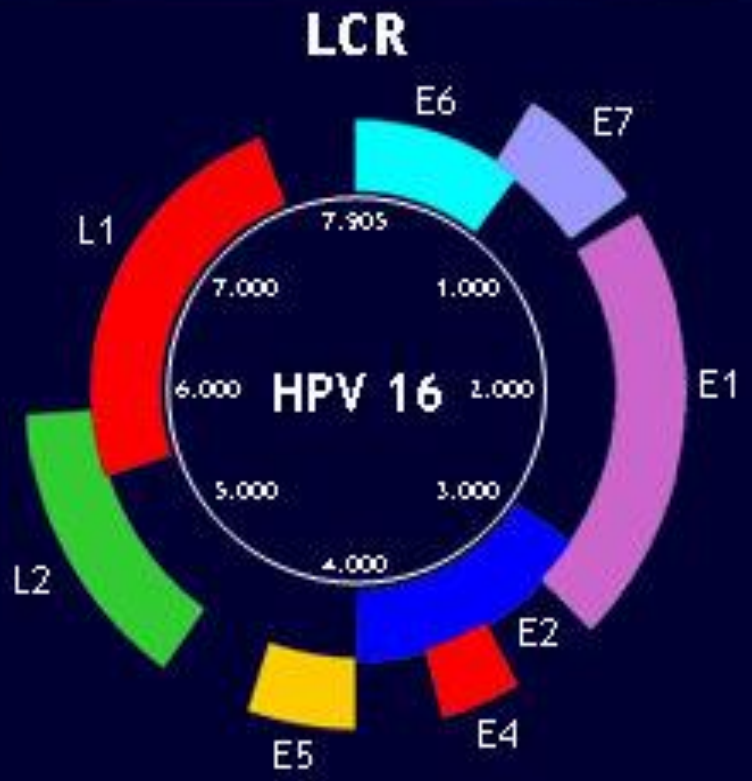


LCR=locus control region; NTPase=nucleoside 5'-triphosphatase; PDGF=platelet-derived growth factor.

Doorbar J. *Clin Sci (Lond)*. 2006;110:525-541.

http://www.medscape.org/viewarticle/558452

Potential Targets

- Replication proteins E1 and E2
  - Targets for early stage disease/dysplasia
- Oncoproteins E6 and E7
  - Targets for advanced stage disease
- Capsid proteins L1 and L2
  - Prophylactic vaccine

Virus-like Particles

- Capsid outer coat
  - L1 (80%)
  - L2 (20%)
- Structural proteins produced to allow shedding of HPV virion after replication

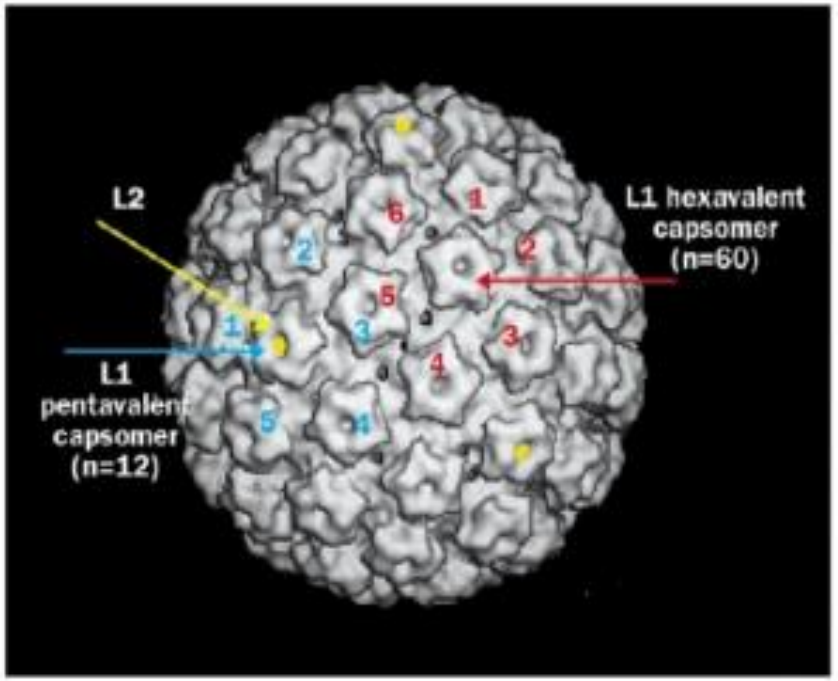
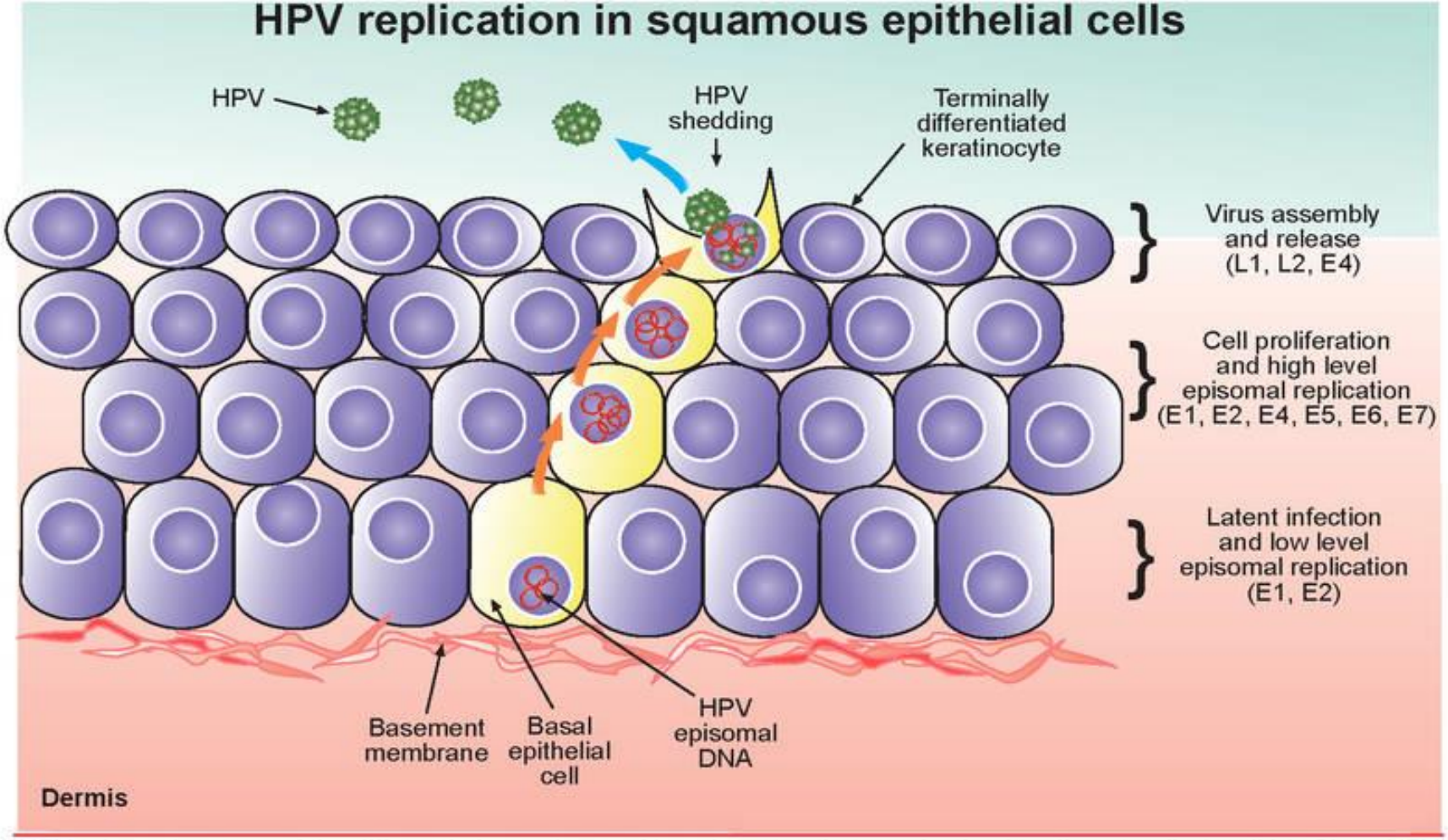


Figure 3. Structure of a HPV virus-like particle. A three-dimensional reconstruction of a cryoelectron micrograph (cryEM) of a virus-like particle (VLP) is shown. The VLP is composed of 60 hexavalent capsomers and 12 pentavalent capsomers, all consisting of pentamers of L1. The L2 protein is not visible by cryEM but is thought to be associated with the pentavalent capsomers, and have been coloured in yellow.

http://www.slideshare.net/terrybear11/hpv-vaccines



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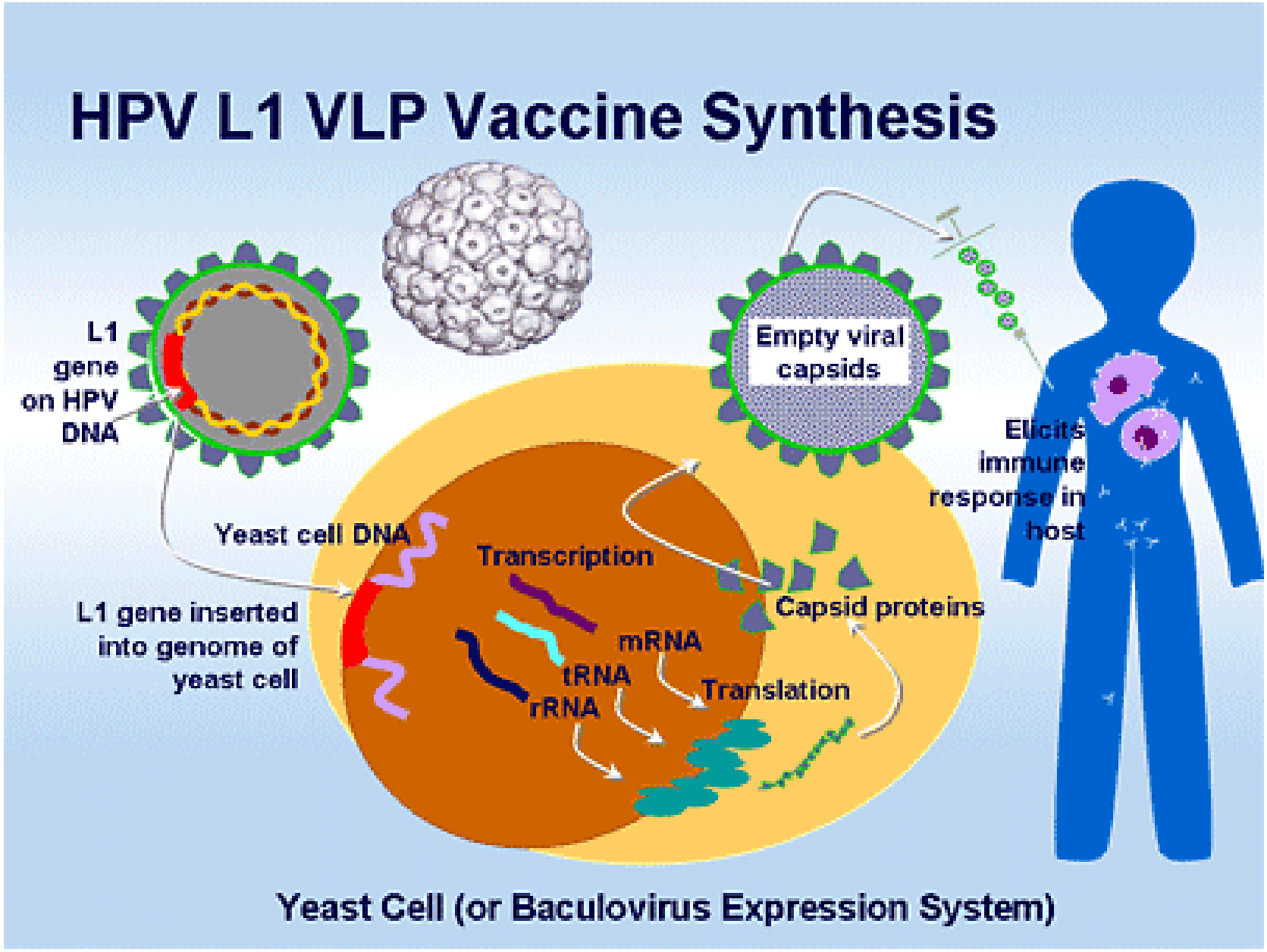
immunopaedia.org

http://immunopaedia.org.za/index.php?id=799



http://www.medscape.org/viewarticle/533104

Phase II Trials

Monovalent	A Controlled Trial of a Human Papillomavirus ***Type 16 Vaccine*** (Nov 2002, NEJM)	Median FU 17.4 mths
Bivalent	Efficacy of a ***Bivalent*** L1 Virus-Like Particle Vaccine in Prevention of Infection with HPV ***Type 16 and 18*** in Young Women: A Randomised Controlled Trial (Nov 2004, Lancet)	Up to 27 mths
Quadrivalent	Prophylactic ***Quadrivalent HPV (Types 6,11,16 and 18)*** L1 Virus-Like Particle Vaccine in Young Women: A Randomised Double-Blind Placebo-Controlled Multicenter Phase II Efficacy Trial (May 2005, Lancet Oncology)	36 mths
Monovalent	Efficacy of Human ***Papillomavirus-16*** Vaccine to prevent Cervical Intraepithelial Neoplasia (Jan 2006, Obstetrics & Gynecology)	48 mths
Bivalent	Sustained efficacy up to 4.5 years of a ***Bivalent*** L1 virus-like particle vaccine against human papillomavirus ***Types 16 and 18***: follow-up from a randomised control trial (15 April 2006, Lancet)	4.5 years
Quadrivalent	High Sustained efficacy of a prophylactic quadrivalent human papillomavirus ***types 6/11/16/18*** L1 virus-like particle vaccine through 5 years of follow-up (Nov 2006, British Journal of Cancer)	5 years

http://www.slideshare.net/terrybear11/hpv-vaccines

Phase III Trials

Quadrivalent (Gardasil)	Quadrivalent Vaccine against Human Papillomavirus to Prevent **Anogenital Diseases** (May 2007, NEJM) (FUTURE I Trial)	N=5455 Average 3 yrs
	Efficacy of a quadrivalent prophylactic human papillomavirus (types 6,11,16 and 18) L1 virus-like particle vaccine against high-grade vulval and vaginal lesions: a **combined analysis of 3 randomised clinical trials** (May 2007, The Lancet)	N=18174 Mean FU 3 yrs
Quadrivalent (Gardasil)	Quadrivalent Vaccine against Human Papillomavirus to Prevent High-Grade **Cervical** Lesions (May 2007, NEJM) (FUTURE II Trial)	N=12167 Average 3 yrs
	Efficacy of prophylactic human papillomavirus L1 virus-like particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3 and adenocarcinoma in situ: a **combined analysis of four randomised clinical trials** (June 2007, The Lancet)	N=20583 Mean FU 3 yrs
Bivalent (Cervarix)	Efficacy of a prophylactic adjuvanted bivalent L1 virus-like particle **types 16 and 18** in young women: an interim analysis of a phase III double-blind, randomised controled trial (June 2007)	N=18644 Mean FU 14.8 mths

http://www.slideshare.net/terrybear11/hpv-vaccines

Gardasil ®

- HPV 6 & 11 – Genital Warts
  - 90% of genital warts
- HPV 16 & 18 – Cervical Cancer
  - 70% of cervical cancers
- Approved June 8, 2006

Ceravix ®

- HPV 16 & 18
  - 70% of cervical cancers
  - Offers cross-protection against other strains
    - HPV 45, 31
  - AS04 – boost immune system response
- Approved October 16, 2009

Gardasil-9 ®

- HPV 6 & 11
  - 90% of genital warts
- HPV 16, 18, 31, 33, 45, 52, 58
  - 90% of cervical cancers
- Approved in December 2014

What About Other Cancers?

Burden of Disease Associated with HPV Vaccine Types

	HPV Type	Cervical Cancer	All HPV-Associated Cancers	Anogenital Warts	
Gardasil	6			90%	Gardasil 9
	11				
	16	66%	64%		
	18				
	31	15%	10%		
	33				
	45				
	52				
	58				

Who Recommends Getting Routine Vaccination?

- Many medical and professional organizations recommend getting vaccinated to protect against HPV infection and cervical cancer.

- The U.S. Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP).
  - This is the group that looks at all the studies and then makes recommendations on what vaccines will be paid for by the "Vaccines for Children Program" (VFC).

and…

Foundation for Women's Cancer, Vaccines to Prevent HPV-Associated Diseases (2013)

- The American Cancer Society
- The American College of Obstetricians and Gynecologists
- The American Academy of Pediatrics
- The American Academy of Family Physicians
- The Society of Gynecologic Oncology
- American College of Nurse-Midwives
- American Medical Women's Association
- American Social Health Association
- American Society for Cytotechnology
- Association of Reproductive Health Professionals
- Association of Women's Health, Obstetric and Neonatal Nurses
- Coalition of Labor Union Women
- National Alliance for Hispanic Health
- National Asian Women's Health Organization
- National Black Nurses Association
- National Cervical Cancer Coalition
- National Cancer Institute
- National Coalition for Cancer Survivorship
- National Council of La Raza
- National Education Association Health Information Network
- National Family Planning and Reproductive Health Association
- Native WEB
- Office on Women's Health, U.S. Department of Health and Human Services
- Planned Parenthood Federation of America
- Prevent Cancer Foundation
- Society of Gynecologic Nurse Oncologists
- Society for Women's Health Research
- Women In Government

Foundation for Women's Cancer, Vaccines to Prevent HPV-Associated Diseases (2013)

Vaccination Schedule

- The vaccination is given over 3 visits.
  1) Today
  2) In 1-2 months
  3) About 4 months after the second visit.

- It is not known at this time whether booster shots will be needed.

Today – Month 0

Vaccination 1

Month 1- 2

Vaccination 2

Month 6

Vaccination 3

Vaccination Complete

Follow-up Pap tests

Foundation for Women's Cancer, Vaccines to Prevent HPV-Associated Diseases (2013)

Who Should Get Vaccinated?

- **<u>Girls & Boys 11–12</u>:** are recommended to receive the vaccine.
  - Girls as young as age 9 can get vaccinated.

- **<u>Women & Men 13–26</u>:** are recommended to get vaccinated if they didn't get it when they were younger.
  - The benefit of the vaccine may be lower depending on prior HPV exposure.

Foundation for Women's Cancer, Vaccines to Prevent HPV-Associated Diseases (2013)

Why So Young?

- Vaccine effectiveness declines with increased number of sexual partners.

Foundation for Women's Cancer, Vaccines to Prevent HPV-Associated Diseases (2013)

HPV Vaccine

Dispelling the Myths

The vaccine is only for females.

But my child isn't sexually active.

Only people with multiple partners get HPV.

The vaccine causes promiscuity.

The vaccine is only for females.

But ctive.

Only rtners

The vaccine causes promiscuity.

Sexual Activity & Promiscuity

Sexual Activity–Related Outcomes After Human Papillomavirus Vaccination of 11- to 12-Year-Olds

WHAT'S KNOWN ON THIS SUBJECT: Concerns persist about sexual disinhibition after human papillomavirus (HPV) vaccination of preteenage girls. Self-reported surveys have indicated few anticipated behavior changes after HPV vaccination. Little is known about sexual activity–related clinical outcomes after HPV vaccination.

WHAT THIS STUDY ADDS: Utilizing managed care organization electronic data, we evaluated the incidence of adverse outcomes of sexual activity among vaccinated preteenage girls and found little difference between those who received HPV vaccine and those who did not.

AUTHORS: Robert A. Bednarczyk, PhD,[a,b] Robert Davis, MD, MPH,[a] Kevin Ault, MD,[c] Walter Orenstein, MD,[c,d] and Saad B. Omer, MBBS, PhD, MPH[a,b,c,d]

[a]Center for Health Research-Southeast, Kaiser Permanente, Atlanta, Georgia; and [b]Rollins School of Public Health, [c]School of Medicine, and [d]Emory Vaccine Center, Emory University, Atlanta, Georgia

KEY WORDS
human papillomavirus, vaccine, sexual activity, disinhibition

ABBREVIATIONS
CI—confidence interval
HPV—human papillomavirus
ICD-9—*International Classification of Diseases, Ninth Revision*

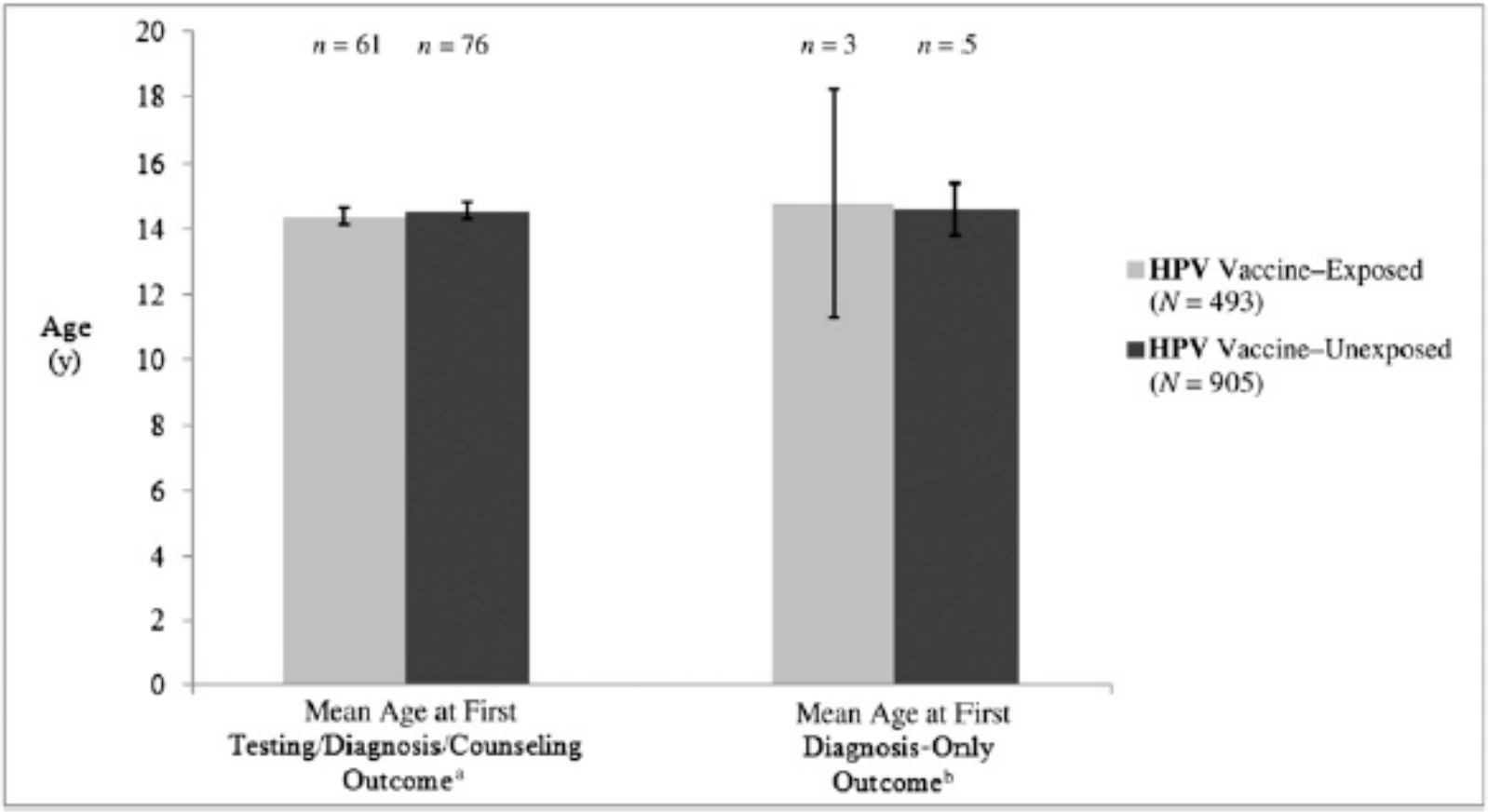


FIGURE 2

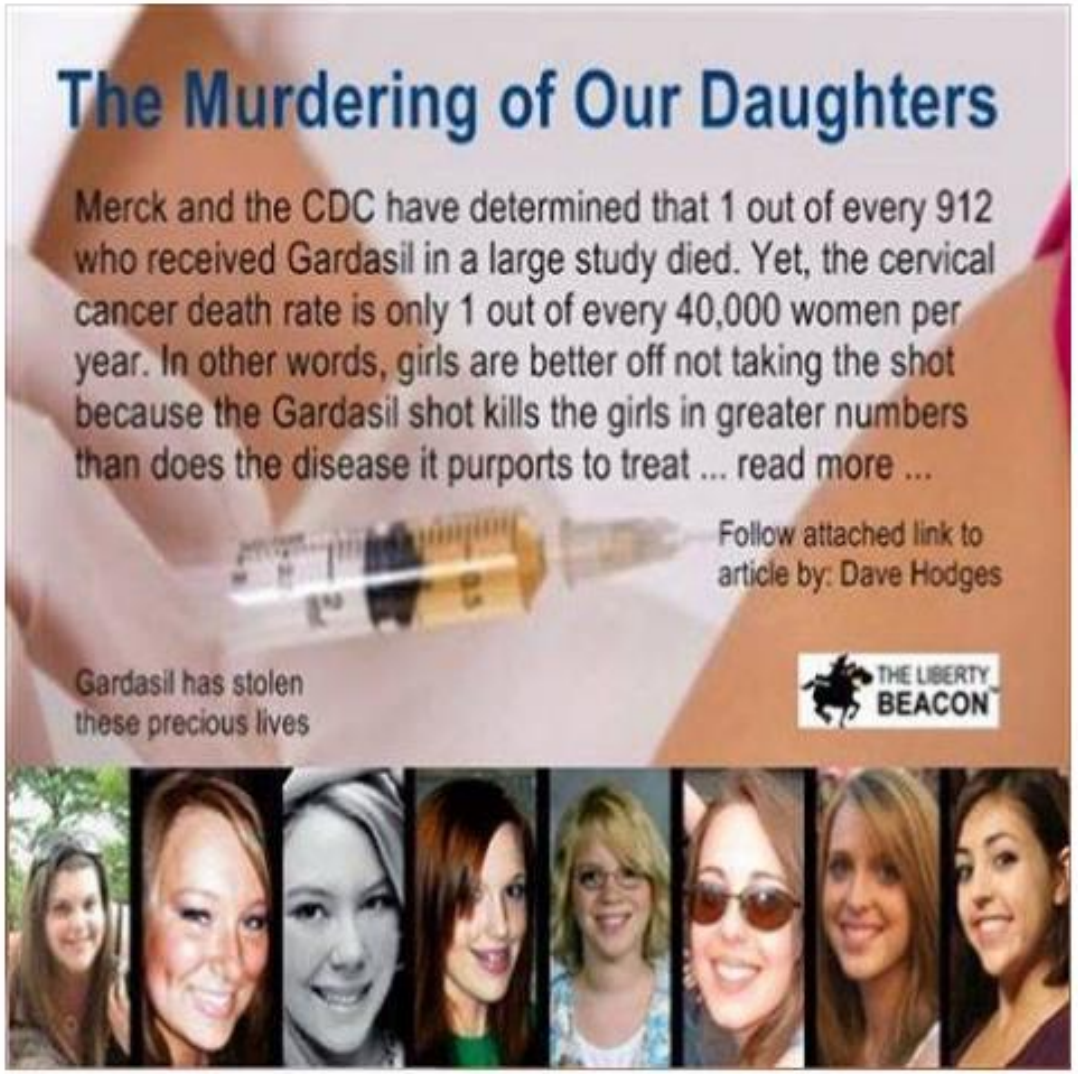
Mean ages at first Testing/Diagnosis/Counseling and Diagnosis-Only outcomes among adolescent girls who received ≥1 adolescent vaccine in a large MCO. Error bars represent 95% CIs for the mean. [a] *t* test $P = .325$; [b] *t* test $P = .818$.

Bednarczyk et al. Pediatrics (2012)

Lead Developer Of HPV Vaccines Comes Clean, Warns Parents & Young Girls It's All A Giant Deadly Scam

Dr. Diane Harper was a leading expert responsible for the Phase II and Phase III safety and effectiveness studies which secured the approval of the human...

DAILYSECRETS.PW


The Murdering of Our Daughters
Merck and the CDC have determined that 1 out of every 912 who received Gardasil in a large study died. Yet, the cervical cancer death rate is only 1 out of every 40,000 women per year. In other words, girls are better off not taking the shot because the Gardasil shot kills the girls in greater numbers than does the disease it purports to treat ... read more ...
Follow attached link to article by: Dave Hodges
THE LIBERTY BEACON
Gardasil has stolen these precious lives

1 in 3 **doctors** 'don't **recommend** the cancer-preventing HPV shot to ...
Daily Mail - Jan 4, 2016
Yet, a survey of nearly 600 **doctors** suggested that **one-third** don't ... However, they were most likely to **recommend** the vaccine - and give the ...

CDC recommends HPV Vaccines for boys
KXAN.com - Jan 5, 2016

YOUR HEALTH

Doctors, Not Parents, Are The Biggest Obstacle To The HPV Vaccine

October 22, 2015 · 12:55 PM ET

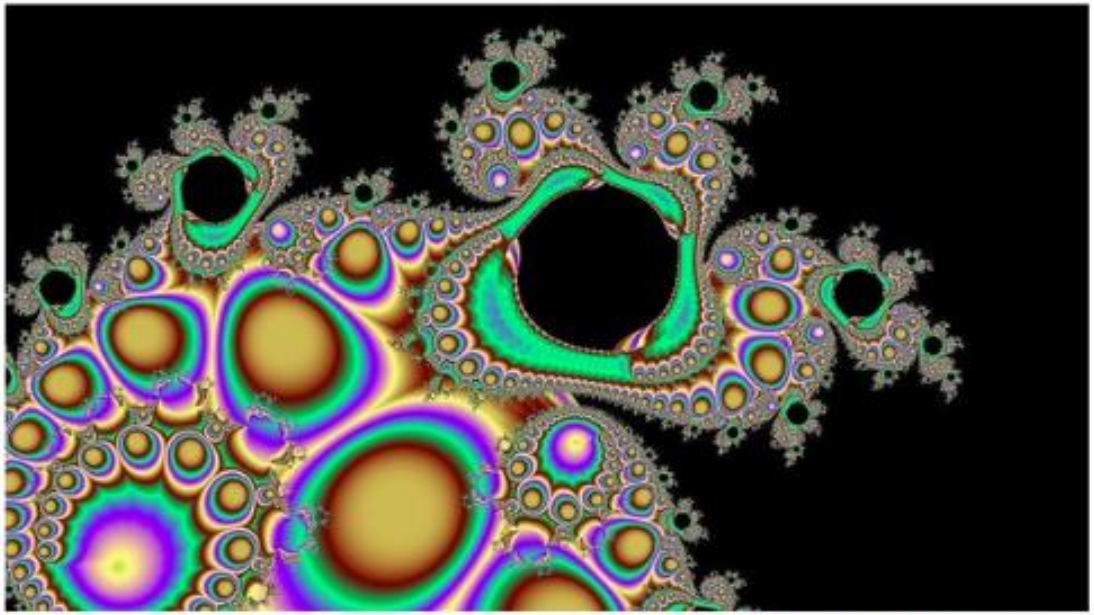
Pediatrics
February 2016, VOLUME 137 / ISSUE 2

Primary Care Physicians' Perspectives About HPV Vaccine

Mandy A. Allison, Laura P. Hurley, Lauri Markowitz, Lori A. Crane, Michaela Brtnikova, Brenda L. Beaty, Megan Snow, Janine Cory, Shannon Stokley, Jill Roark, Allison Kempe

Abstract

BACKGROUND AND OBJECTIVES: Because physicians' practices could be modified to reduce missed opportunities for human papillomavirus (HPV) vaccination, our goal was to: (1) describe self-reported practices regarding recommending the HPV vaccine; (2) estimate the frequency of parental deferral of HPV vaccination; and (3)identify characteristics associated with not discussing it.



Pediatricians Association Admits HPV Vaccine Causes Ovarian Failure

January 28, 2016 by Gary TruthKings Vaccine

ADVERTISEMENT

The HPV vaccine is heavily pushed to both teen girls and boys. Even though countries such as Japan won't formally have stated that they don't want to support it, the United States continues to massively push this vaccine despite all the push back world-wide. The HPV money grab by pharmaceutical companies is blatant and unchecked. Well, now things just got a whole lot worse: The American College Of Pediatricians has announced that the HPV vaccine is "possibly" associated with ovarian cancer. You can view the document here.

But I heard about these side effects…

- Yes, there are side effects:
  - Arm soreness
  - Fainting
  - Myalgias
- But there is no proof of the vaccine causing:
  - Autism
  - Serious morbidity and mortality
  - Sexual promiscuity

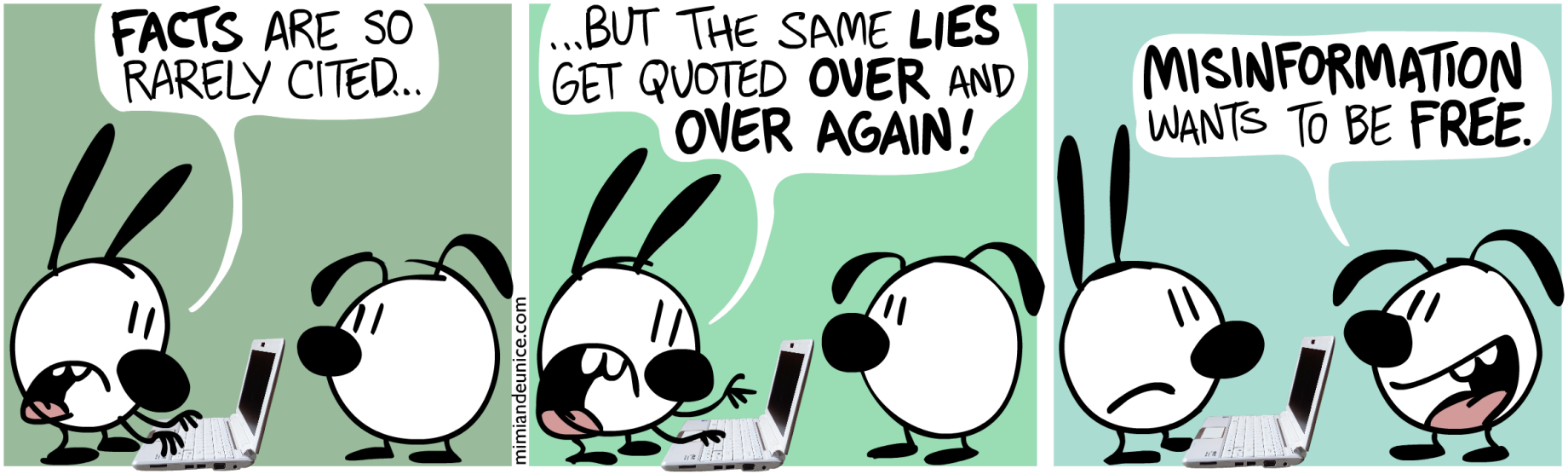
Table 4: Rates (%) of Solicited and Unsolicited* Injection-Site and Systemic Adverse Reactions among Individuals Previously Vaccinated with GARDASIL Who Received GARDASIL 9 or Saline Placebo (Girls and Women 12 through 26 Years of Age) (Study 4)

	GARDASIL 9 N=608	Saline Placebo N=305
Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)		
Injection-Site Pain	90.3	38.0
Injection-Site Erythema	42.3	8.5
Injection-Site Swelling	49.0	5.9
Oral Temperature ≥100.0°F†	6.5	3.0
Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)		
Injection-Site Pruritus	7.7	1.3
Injection-Site Hematoma	4.8	2.3
Injection-Site Reaction	1.3	0.3
Injection-Site Mass	1.2	0.7
Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)		
Headache	19.6	18.0
Pyrexia	5.1	1.6
Nausea	3.9	2.0
Dizziness	3.0	1.6
Abdominal pain, upper	1.5	0.7
Influenza	1.2	1.0

The data for GARDASIL 9 and saline placebo are from Study 4 (NCT01047345).
*Unsolicited adverse reactions reported by ≥1% of individuals
N=number of subjects vaccinated with safety follow-up
†For oral temperature: number of subjects with temperature data GARDASIL 9 N=604; Saline Placebo N=304

http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf

Misinformation – Get the Facts!



HPV Vaccine

International Success Stories


Papua New Guinea
Indonesia
Timor Leste
Indian Ocean
Coral Sea
Australia
Sydney
Canberra
Melbourne
Southern Ocean
Tasmania

Australia

- Government funded National HPV Vaccination Program started in April 2007
  - School based program for age 12-13
  - Time limited catchup for age 14-26 until 2009
- Expanded to males in 2010

- Over 70% of females have been vaccinated

Australia: 5 year results

- Reduced prevalence of vaccine HPV genotypes (6, 11, 16, 18) from 28.7% to 6.7%
  - Additionally lowered non-vaccine HPV oncotypes in vaccinated women (37.6% to 30.8%)

Tabrizi et al, J Infect Diseases 2012

- Large declines in women newly diagnosed with genital warts (baseline around 9%)
  - 11.5% to 0.85% under age 21
  - 11.3% to 3.1% from age 21-30

Ali et al, BMJ 2013

HPV Vaccine

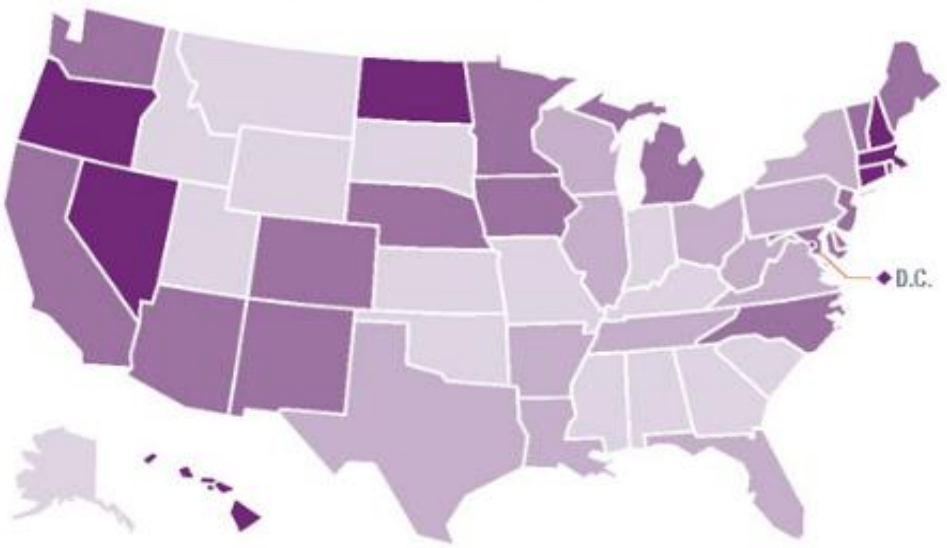
What We Can Do

NATIONWIDE 6 OUT OF 10 GIRLS HAVE STARTED THE HPV VACCINE SERIES

National coverage is 63%
Coverage by state:

- 59% or less
- 60-64%
- 65-69%
- 70% or greater

Percentage of adolescent girls who have received one or more doses of HPV vaccine*

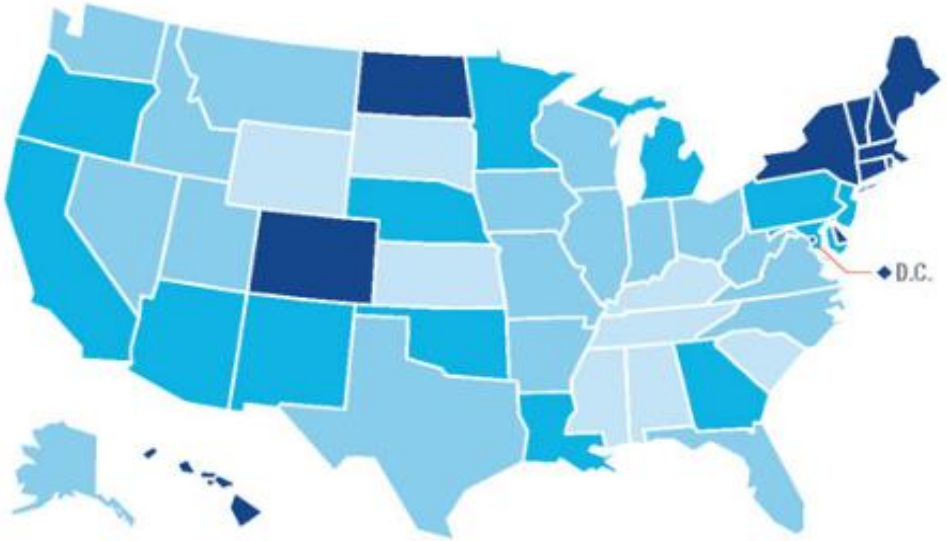


NATIONWIDE 5 OUT OF 10 BOYS HAVE STARTED THE HPV VACCINE SERIES

National coverage is 50%
Coverage by state:

- 39% or less
- 40-49%
- 50-59%
- 60% or greater

Percentage of adolescent boys who have received one or more doses of HPV vaccine*



http://www.cdc.gov/hpv/infographics/vacc-coverage.html

What We Can Do

- Education, education, education
- Remember the schedule
- Recognize it’s not about sex!
- Compulsory vaccinations

Thank You!